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Transdermal therapeutic system for administration of candesartan

Background of The Invention

The invention relates to an active ingredient-containing transdermal system for administration of candesartan and/or its pharmaceutically suitable esters and/or salts.

Candesartan (2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid) is a highly specific, non-peptide angiotensin II receptor antagonist. It has a high specificity and a strong affinity for the AT_1 receptor and a long duration of binding, and thus a long-lasting activity. Candesartan is mainly used to treat essential hypertension (non-organ-related high blood pressure), heart diseases, strokes, nephritis (EP-0459136 B1) and left ventricular hypertrophy.

On oral administration, the ester (candesartan cilexetil) of candesartan and 1-(cyclohexyloxycarbonyl-oxy)ethanol is used as prodrug (EP-0459136 B1) in order to ensure the stability necessary for passing through the stomach and thus increase the bioavailability (Kubo, K.; Kohara, Y. and co-workers; J. of Medicinal Chemistry; 36 (16) 2343-2349/1993). This ester is converted completely by ester hydrolysis in the gastrointestinal tract into its active form candesartan which is 30% more active than the ester. Candesartan is then extensively distributed in the tissue and

in blood vessels. The elimination of candesartan from the blood vessel walls takes place considerably more slowly than from the plasma, resulting in the long-lasting effect. Candesartan is partly metabolized further to inactive metabolites in the liver. Candesartan and its metabolites are then, after hepatobiliary passage, excreted with feces and urine. The ester side chain of candesartan cilexetil which is eliminated in the intestine is absorbed and distributed in the tissue mainly as cyclohexanol. In the liver there is then degradation to cyclohexanediol, cyclohexanetriol and other degradation products. The bioavailability of candesartan in this case is only 14%. The maximum therapeutic effect on oral intake is reached after 4 weeks because a gradual reduction in blood pressure takes place through the slow occupation of the receptors.

To date candesartan cilexetil has been administered exclusively orally or intravenously. Since candesartan is degraded by gastric acid during passage through the stomach, either the active ingredient must be esterified or an elaborate dosage form, such as, for example, an enteric coating, must be produced. This results in additional costs both for the machines and workforce and for the additionally required material. The bioavailability of active ingredients on oral administration is frequently unsatisfactory. In this case, it is only 14%. The hepatic metabolism of the active ingredient on first passage through the liver may lead to

unwanted concentration conditions and toxic byproducts, and to a reduction in the effect.

The object of the present invention is now to provide a transdermal system for systemic administration of candesartan and/or one of its pharmaceutically suitable esters or salts, the intention being to avoid the disadvantages of oral or intravenous administration forms used to date.

The Invention

It has now been found, surprisingly, that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached. The possibility of using the active ingredient candesartan and/or its pharmaceutically suitable esters and salts, which display a direct systemic effect, makes it possible to increase considerably the bioavailability and greatly reduce the dose level. The stress on the body and the adverse effect on the liver due to the metabolism can thus be considerably reduced. The use of a transdermal therapeutic system makes controlled delivery of active ingredient possible, so that large blood plasma variations can be avoided and a constant blood plasma level can be guaranteed even for several days. The optimal effect of the active ingredient is thus achieved conveniently and reliably. The maximum therapeutic effect is reached after only 3 weeks.

It is likewise to be regarded as advantageous that the use of plasters is simple and convenient by comparison with oral or intravenous administration. Since the system is applied externally, it can carry out its intended function in this way for a very long time without being changed. This is completely impossible with oral systems because they leave the body through the digestive tract after one day at the longest. In addition, it is simpler and more pleasant for the patient to have ~~to have~~ to think of taking the medicine only 1-2 times a week instead of having to take a tablet once a day.

The object on which the invention is based is now achieved by a transdermal therapeutic system with a content of candesartan and/or one of its pharmaceutically suitable esters or salts, in particular by candesartan and/or candesartan cilexetil.

Possible and suitable salts of candesartan are, in particular, alkali metal salts such as, for example, the potassium, sodium and lithium salts, and the ammonium salt.

Candesartan and/or one of its pharmaceutically acceptable esters or salts as active ingredient can moreover be administered in combination with other known active ingredients, especially diuretics and Ca channel blockers, for example hydrochlorothiazide (HCTZ) or amlodipine. These active ingredients exert an additive antihypertensive effect.

The transdermal therapeutic system according to the invention may be in the form of a plaster. This plaster may be a matrix or membrane system which has an impermeable covering layer and a detachable protective layer. A suitable constituent of the impermeable covering layer is polyester, polypropylene, polyurethane or polyethylene, each of which may be metalized or pigmented if required. Suitable for the detachable protective layer are polyester, polypropylene, polysiloxane, polyacrylate, ethylene/vinyl acetate, polyurethane, polyisobutene or paper with silicone and/or polyethylene coating.

The matrix plaster may consist of an impermeable covering layer, of one or more than one self-adhesive matrix layer which contains the active ingredient and/or one of its pharmaceutically suitable esters or salts and, where appropriate, other active ingredients and/or permeation promoters and/or amino acids, or of a matrix layer which is coated with a contact adhesive, and of a detachable protective layer. The active ingredient present in the matrix may be candesartan and/or its pharmaceutically suitable ester or salts and, in the case of combination, additionally other active ingredients such as Ca channel blockers or diuretics, for example amlodipine or HCTZ.

It is possible to use for the matrix the matrix formers usual in medicine, such as polyacrylate, silicone, polyisobutylene, rubber, rubber-like synthetic homo-, co- or

block polymers, butyl rubber, styrene/isoprene copolymer, polyurethanes, copolymers of ethylene, polysiloxanes or styrene/butadiene copolymer.

A further embodiment of the invention is in the form of a membrane system. This may consist of an impermeable covering layer, of an active ingredient-containing reservoir or of a reservoir layer, of a semipermeable membrane, of an optional contact adhesive layer and of a detachable protective layer. The reservoir may contain candesartan and/or one of its pharmaceutically suitable esters or salts, where appropriate other active ingredients and/or permeation promoters, stabilizers, emulsifiers, thickeners and/or conventional membrane system or reservoir plaster aids. The reservoir or the reservoir layer is located between the covering layer and the membrane. Gel formers which can be used if required are methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxyvinyl polymer, sodium glyoxylate, carboxymethylcellulose or a mixture of these.

The membrane, which normally consists of inert polymers, in particular based on polypropylene, polyvinyl acetate, polyamide, ethylene/vinyl acetate copolymers or silicone, may, depending on the pore size, have a controlling effect on release of active ingredient.

It is possible to choose for the contact adhesive layer of the matrix or membrane system according to the invention which is described above a pressure-sensitive

adhesive, for example a polyurethane-based, polyisobutylene-based, polyvinyl ether-based, silicone-based or acrylate-based one.

The silicone-based adhesive may be a silicone adhesive which is based on two main constituents, a polymer or adhesive, in particular polysiloxane, and a tack-increasing resin. The polysiloxane adhesive is usually prepared with a crosslinker for the adhesive, typically with a high molecular weight polydiorganosiloxane, and with the resin, in order to afford a three-dimensional silicate structure via an appropriate organic solvent. Addition of the resin to the polymer is the most important factor for altering the physical properties of the polysiloxane adhesives; cf., for example, Sobieski, et al., "Silicone Pressure Sensitive Adhesives", Handbook of Pressure Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Another example of a pressure-sensitive silicone-based adhesive is trimethylated silicon dioxide which has been treated with polydimethylsiloxane with terminal trimethylsiloxy groups.

The acrylate-based adhesives can be any homopolymer, copolymer or terpolymer consisting of various acrylic acid derivatives.

Thus, the acrylate polymers can be polymers of one or more monomers of acrylic acids and other copolymerizable

monomers. The acrylate polymers may additionally comprise copolymers of alkyl acrylates and/or alkyl methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. It is possible by altering the amount of each type of monomer added to alter the cohesive properties of the acrylate polymers resulting therefrom. In general, the acrylate polymer consists of at least 50% by weight of an acrylate, methacrylate, alkyl acrylate or alkyl methacrylate monomer, 0 to 20% of a functional monomer copolymerizable with acrylate, and 0 to 40% of another monomer.

Acrylate monomers which can be used with acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate are listed below.

Thus, functional monomers copolymerizable with the above-mentioned acrylates, methacrylates, alkyl acrylates or alkyl methacrylates can be employed, for example acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminomethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate.

Further details and examples of pressure-sensitive acrylates suitable for the invention are described in Satas Handbook of Pressure Sensitive Adhesive Technology "Acrylic Adhesives", 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Permeation promoters which can be used are monohydric and/or polyhydric aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols each with up to 8 C atoms, for example ethanol, 1,2-propanediol, dexpanthenol and/or polyethylene glycol; alcohol/water mixtures; saturated and/or unsaturated fatty alcohols each with 8-18 C atoms; terpenes; for example cineol, carveol, menthone, terpineol, verbenone, menthol, limonene, thymol, cymene, terpinen-4-ol, neomenthol, geraniol, fenchone; mixtures of terpenes and ethanol and/or propylene glycol; tea tree oil; saturated and/or unsaturated cyclic ketones; alkyl methyl sulfoxides; saturated and/or unsaturated fatty acids each with 8-18 C atoms; the esters and salts thereof; natural vitamin E; synthetic vitamin E and/or vitamin E derivatives; sorbitan fatty acid esters and ethoxylated sorbitan fatty acid esters; Azone (laurocapram); Azone mixed with alcohols; urea; 1-alkylpyrrolidone; block copolymers of polyethylene glycol and dimethylsiloxane with cationic groups at one end; folate-polyethylene glycol liposome, proliposome; polyoxyethylene 10 stearyl ether; mixture of polyoxyethylene 10 stearyl ether and glyceryl dilaurate; dodecyl 2-(N,N-dimethylamino)propanoltetra-

decanoate and/or dodecyl 2-(N,N-dimethylamino)propionate; N-acetylprolinate esters with more than 8 C atoms; nonionic surfactants, for example lauryl ethers, esters of polyoxyethylene; ethosome (phospholipid vesicle); dimethyl(arylimino)sulfurane; mixture of oleic acid analogs and propylene glycol; mixture of padimate O, octyl salicylate, octyl methoxycinnamate and laurocapram and/or mixtures of all these components.

The invention is explained in detail by the following examples without, however, restricting the scope of the invention thereby.

Example 1 (matrix plaster)

11.1 g of candesartan cilexetil are dissolved in 75 g of extra pure acetone, and 8 g of Copherol F1300 are added. The clear solution is added to 169 g of an approx. 36% strength acrylate copolymer (Duro-Tak 387-2353, Nat. Starch & Chemical B.V.) and stirred. The homogeneous solution is spread on a siliconized polyester sheet (for example 75 µm) or on siliconized paper and dried at 35°C to 85°C to result in a matrix dry weight of 80 ± 10% g/m^2. The detachable protective layer (for example polyester 15 µm) is then laminated onto the matrix side.

TTS with an area of 20 cm^2 are punched out.

A plaster of this size contains 16 mg of candesartan and 16 mg of α-tocopherol.

Example 2 (reservoir plaster) (see drawing)

Firstly 138.4 g of candesartan cilexetil are dissolved in 861.6 g of a mixture of ethanol abs. 65% (V/W), Copherol F1300 10% (V/W) and hydroxypropylcellulose, 1% (V/W) with stirring. This mixture is the active drug solution for the reservoir. The reservoir is charged with 400 ± 5% mg of the active drug solution.

The transdermal therapeutic system (see drawing) consists firstly of the optional adhesive layer which forms the adhesive ring. Onto this layer is applied a heat-sealable, impermeable covering layer. On the side facing the skin, the reservoir is affixed to the covering layer and sealed with a microporous EVA membrane (Cotran 9702, 3M). A siliconized PET sheet serves as detachable protective layer.

A plaster thus contains:

Candesartan cilexetil	55.36 mg (equivalent to 40 mg of candesartan)
Copherol F1300	40 mg
Ethanol abs.	300.64 mg
Hydroxypropylcellulose	4 mg